

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/14, B01D 9/02, A61K 9/72		A1	(11) International Publication Number: WO 96/32095 (43) International Publication Date: 17 October 1996 (17.10.96)
<p>(21) International Application Number: PCT/SE96/00479</p> <p>(22) International Filing Date: 12 April 1996 (12.04.96)</p> <p>(30) Priority Data: 9501384-3 13 April 1995 (13.04.95) SE</p> <p>(71) Applicant (<i>for all designated States except US</i>): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): JAKUPOVIC, Edib [SE/SE]; Smultronvägen 7, S-155 31 Nykvarn (SE). TROFAST, Jan [SE/SE]; Vapenkroken 34, S-226 47 Lund (SE).</p> <p>(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p>			
<p>Published <i>With international search report.</i></p>			

(54) Title: PROCESS FOR THE PREPARATION OF RESPIRABLE PARTICLES

(57) Abstract

A process for producing a pharmaceutical powder for inhalation comprising crystalline particles of an inhalation compound, comprising dissolving an inhalation compound in a solvent; and introducing the solution containing the inhalation compound in droplet form or as a jet stream, into an anti-solvent which is miscible with the solvent and which is under agitation.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

PROCESS FOR THE PREPARATION OF RESPIRABLE PARTICLES

Field of the invention

This invention relates to a process for preparing a pharmaceutical powder for inhalation, which powder comprises crystalline particles of an inhalation compound, in particular particles of mass median diameter 10 μ m or less.

Background of the invention

Inhalation of dry powders has been recognised as a valuable method for the administration of pharmacological agents and in particular those which are useful in the treatment of diseases of the respiratory tract. However, the utility of the method has been limited by the difficulty in making appropriate doses available to the lower respiratory tract of the patient. In general only a relatively small proportion of any nominal dose will reach the lower respiratory tract of the inhaling patient; the remainder may remain in the inhaler device or be deposited in the mouth and throat of the patient.

One major factor determining the proportion of inhalable drug which will reach the lower respiratory tract of a patient is the particle size distribution of the particles emerging from the inhaler device. This particle size distribution is in turn dependent both on the construction and function of the inhaler, and the powder formulation. The present application is concerned with the nature of the powder formulation. This should have a high integrity of the crystal structure, or crystal habit (as may be measured using X-ray crystallography techniques, for example), high purity and stability, and a particle size within the respirable particle range.

25

In order to achieve a desired crystal structure and particle size, powder formulations of respirable particles are in general obtained by processes including crystallisation from solution followed by micronisation. However, optimum crystal structure formation and optimum purity may not be obtained in this process, and micronisation has associated problems. Prolonged comminution results in a high energy powder and crystal lattice

defects which may be manifested for example in lower stability, and/or hygroscopicity. As micronisation results in some amorphous character on the surface of the obtained particles, a "conditioning" step is necessary in order to obtain a particle considered to be completely crystalline. International patent applications PCT/SE91/00186 (WO 92/18110) and PCT/SE94/00780 (WO 95/05805) describe methods of conditioning substances in order to obtain crystalline products. It is an object of the present invention to provide a process for the production of crystalline respirable particles which avoids the necessity for post-crystallisation micronisation.

10 European Patent no. 437451 discloses a process for producing finely divided solid crystalline powders, comprising dissolving the solid to be finely divided in a liquid carrier solvent to form an injection solution and adding the injection solution to a volume of anti-solvent, which is a supercritical fluid, liquefied compressed gas or dense vapour, sufficient to precipitate or crystallise the solid.

15 European patent application, publication number 0 542 314 A1, discloses a method of forming microparticles of a material, involving bringing a supercritical anti-solvent gas into contact with a solution of said material in a solvent at a controlled rate operable to expand the solution and precipitate the material. Needles and globules are formed.

20 Neither of the above are directed to powders for inhalation per se, and as they use supercritical media the use of compressed gases and heavy, expensive apparatus is necessitated.

25 US Patent number 5 314 506, again not related to powders for inhalation, describes impinging a jet stream of an organic pharmaceutical compound and a jet stream of an anti-solvent, to precipitate small crystals of the organic pharmaceutical compound. Pressurised blow-cans and elevated temperatures are employed, and the crystals obtained range from flakes of up to 25 microns, to needles, and cubes of less than 3 microns.

EP 0169618 discloses a method for the preparation of water-insoluble organic compounds such as may be used in suspensions for intravenous injection, as non-crystalline particles. The method involves preparing a solution of the compound in a water-miscible organic solvent and infusing an aqueous precipitating liquid into the organic solution, in most cases in the presence of surfactant.

The process of the present invention aims to provide a powder for inhalation comprising crystalline particles of an inhalation compound of mass median diameter less than 10 μm , irrespective of the substance concerned. Thus the process does not require the use of supercritical media nor the processes of micronising and conditioning.

According to the present invention there is provided a process for producing a pharmaceutical powder for inhalation comprising crystalline particles of an inhalation compound, comprising dissolving an inhalation compound to be provided in crystalline particle form in a solvent; and introducing the solution containing the inhalation compound, in droplet form or as a jet stream, into an anti-solvent which is miscible with the solvent and which is under agitation, under non-supercritical conditions.

There is also provided according to the present invention a pharmaceutical powder and a crystalline inhalation compound obtainable by the process of the invention.

Preferably the particles of the inhalation compound of the present invention have a mass median diameter of at least 0.1 μm , more preferably at least 1 μm . Where the powder is intended particularly for oral inhalation, preferably the particles have a mass median diameter of 10 μm or less, preferably 7 μm or less. Most preferably the particles have a mass median diameter of 1-6 μm . By "mass median diameter" is meant that half of the mass of the inhalation compound is made up of particles having a diameter less than the mass median diameter and half of the mass of the inhalation compound is made up of particles having a diameter greater than the mass median diameter. Preferably as much as possible of

the powder consists of particles of diameter 10 μm or less; for example at least 75% or at least 90% of the powder consists of particles of diameter 10 μm or less:

5 The pharmaceutical powder of the present invention may be administered orally or nasally. Where nasal administration is intended the particles of the inhalation compound may have a mass median diameter outside the above preferred ranges.

10 The pharmaceutical powder may comprise a water-soluble inhalation compound, or a water-insoluble inhalation compound.

15 The solution containing the inhalation compound is introduced into the anti-solvent in droplet form or as a jet-stream, for example through a porous filter or one or more nozzles.

20 Through the present invention it is possible to control the size of particles obtained by controlling any or all of parameters such as the concentration of the compound in the solvent, the rate of addition of the solution into the anti-solvent and the intensity of the agitation such that particles within a specific desired particle size range may be obtained. A powder formulation having good physicochemical stability and needing no mechanical micronisation or conditioning is obtained.

25 Medically useful compounds which may be provided in respirable particle form according to the present invention include β_2 -adrenoreceptor agonists, for example salbutamol, terbutaline, rimiterol, fenoterol, reproterol, adrenaline, pirbuterol, isoprenaline, orciprenaline, bitolterol, salmeterol, formoterol, clenbuterol procaterol, broxaterol, picumeterol, TA-2005 ([8-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl)amino)ethyl)-2(1H)-quinolone], mabuterol; anticholinergic bronchodilators, for example ipratropium bromide; glucocorticosteroids, for example betamethasone, fluticasone, budesonide, tipredane, dexamethasone, beclomethasone, fluocinolone, triamcinolone acetonide, mometasone and rofleponide; peptides and proteins, for example insulin, immunomodulators, anti-allergic drugs for example sodium

cromoglycate and nedocromil sodium; expectorants; mucolytics; antihistamines; cyclooxygenase inhibitors; leukotriene synthesis inhibitors; leukotriene antagonists, PLA2 inhibitors, PKC-inhibitors, PAF antagonists and prophylactics of asthma; or pharmacologically acceptable esters and salts and/or solvates thereof. For example
5 salbutamol and terbutaline may be used as the sulphate; fenoterol as the hydrobromide; salmeterol as the xinafoate; formoterol as the fumarate dihydrate; clenbuterol as the hydrochloride; fluticasone as the propionate; and broxaterol as the monohydrochloride.

10 Preferably the medically useful compound is selected from β 2-adrenoreceptor agonists and glucocorticosteroids.

Most preferably the medically useful compound is selected from salbutamol, preferably as the sulphate, salmeterol, preferably as the xinafoate, formoterol, preferably as the fumarate dihydrate, budesonide, terbutaline, preferably as the sulphate, fluticasone,
15 preferably as the propionate, rofleponide, preferably as the palmitate, and other pharmaceutically acceptable esters and salts and/or solvates thereof.

Pharmaceutically acceptable additives e.g., carriers, diluents, and penetration enhancers may also be prepared according to the present invention. For example the process of the
20 present invention may be used to prepare carbohydrates such as lactose, dextrose, melezitose, maltose, mannitol, trehalose and raffinose, as well as salts of fatty acids, bile salts, phospholipids and alkyl glycosides, which may be useful as penetration enhancers. The pharmaceutically acceptable additive may be prepared separately from the medically useful compound, and the powders may then be mixed together, or a powder containing
25 the medically useful compound and additive may be prepared in certain cases, i.e. when the compound and additive have similar solubility's, by dissolving all of the desired substances together in the solvent according to the present invention.

In the process of the present invention, the choice of solvent depends upon the solubility
30 of the compound to be dissolved. Preferably, a substantially saturated or supersaturated

solution is obtained. The anti-solvent should be miscible with the solvent in order that a single-phase solvent mixture is formed and should be such that the dissolved compound is precipitated immediately upon contact therewith.

- 5 The choice of particular solvent and anti-solvent can be made readily by a person skilled in the art considering the solubility characteristics of the compound to be precipitated. In general, water-soluble substances may be dissolved in water or another solvent more polar than the anti-solvent, or a mixture of such solvents, and precipitated with a less polar solvent (the anti-solvent); and substantially water-insoluble substances may be
- 10 dissolved in a less polar solvent and precipitated with water or another "more polar" solvent (the anti-solvent). For example, a water-soluble substance which is dissolved for example in water may be precipitated with an anti-solvent such as ethyl acetate, acetone, methylethyl ketone (2-butanone), isopropanol, or mixtures of for example 10-20% methanol, isopropanol or ethanol with 80-90% (w/w) methylethyl ketone or isopropanol,
- 15 while a less water-soluble substance may be dissolved for example in an organic solvent such as methanol, isopropanol or another alcohol, dimethyl sulphoxide, dimethyl formamide, N'N'-dimethyl acetamide or phenol and precipitated with for example water.

- 20 To maximise the degree of precipitation it is desirable that the solution is added to the anti-solvent at temperatures as low as possible, but low temperatures are not essential for the process of the present invention. Preferably, the solution is added to the anti-solvent at temperatures of below 25 °C, for example at around 0°C or from 0 to 5 °C.

- 25 According to the present invention the solution is preferably added to the anti-solvent through a porous filter having pores of 10 - 160 microns, such as Pyrex Glass Filters of porosity grades 1-4.

The rate of addition may be controlled, for example by using a pump, such as a peristaltic pump when working on a laboratory scale.

In order that the droplet or fine jet, as well as the precipitated compound, is efficiently removed from the porous filter or nozzle, it is necessary for the anti-solvent to be under agitation. The agitation may be achieved in various ways such as by means of mechanical stirring with propellers, turbines, paddles, anchor impellers or Ystral equipment, or by using ultrasound waves on or beside the filter or nozzles.

The precipitated compound may be dried in conventional manner, for example it may be spray-dried, and may be agglomerated and/or spheronised if desired. No conditioning is necessary as the particles obtained are considered to be completely crystalline.

10

The size of the particles obtained according to the present process may be controlled by adjusting the process parameters, as will be evident to a person skilled in the art. For example, decreasing the concentration of compound in the solvent will lead to smaller particles, and adjusting the rate of addition and/or agitation will alter the particle size by 15 altering the size of the droplet from which the compound is precipitated. Any one, several, or all of the process parameters may be adjusted in order to obtain a particular particle size range. The optimal process parameters in each case may be determined by a person skilled in the art using routine experimentation.

20 Various methods may be employed in order to monitor the crystallinity of the respirable particles of the present invention. Such methods, which are all well known to the skilled person in the art, include isothermal micro calorimetry, BET gas adsorption, X-ray powder diffraction and differential scanning calorimetry (DSC). For example during a recrystallisation a large amount of heat is evolved and by monitoring the calometrical 25 signal the sample may be checked for any amorphous content.

The following Examples are intended to illustrate, but not limit, the scope of the present invention. The particle sizes given were measured using a Malvern Master Sizer instrument.

Example 1

A solution of budesonide (15 g) in methanol (300 ml) was added to water (450 ml) at a temperature of 0°C, through a glass filter, Pyrex porosity grade 3 (pore index 16-40 microns), and with stirring with ultraturrax equipment.

5

A slurry was obtained, containing particles with a mass median diameter (MMD) of 2.2 microns. 90% of the particles had a diameter of below 5.3 μ m. The slurry was spray dried using a commercially available spray-dryer (Büchi 190), to give a budesonide powder consisting of particles of MMD 2.9 microns having no amorphous character, i.e., crystalline 10 particles, determined using powder X-ray measurements. 90% of the particles had a diameter of below 5.7 μ m.

The particles obtained could be agglomerated for use in dry powder inhalers.

15 Example 2

A solution of budesonide (2.35 g) in methanol (60 ml) was added to water/ice (200 ml) at a rate of 1 ml/min, through a glass filter with a porosity of 40-90 microns, and with stirring with ultraturrax equipment (4.5). The obtained slurry contained budesonide crystalline particles of MMD 2.79 microns. 90% of the particles had a diameter of below 20 6.0 μ m.

Example 3

A solution of budesonide (1.5 g) in methanol (80 ml) was added to water/ice (300 ml) at a rate of 1 ml/min, through a Pyrex glass filter of porosity grade 2 (40-100 microns), and 25 with stirring with ultraturrax equipment (4.5). The obtained slurry contained budesonide crystalline particles of MMD 2.60 microns. 90% of the particles had a diameter of below 6.0 μ m.

Example 4

The procedure of Example 3 was repeated using a Pyrex glass filter of porosity grade 4 (10-16 microns). The obtained slurry contained budesonide crystalline particles of MMD 2.49 microns. 90% of the particles had a diameter of below 6.0 μ m.

5

Example 5

A solution of budesonide (3 g) in methanol (90 ml) was added to water/ice (300 ml) at a rate of 1 ml/min, through a Pyrex glass filter of porosity grade 1 (100-160 microns), and with stirring with ultraturrax equipment (4.5). The obtained slurry contained budesonide 10 crystalline particles of MMD 4.76 microns. 90% of the particles had a diameter of below 9.6 μ m.

Example 6

A solution of budesonide (1.2 g) in methanol (50 ml) was added via a peristaltic pump and 15 through a glass filter, Pyrex no. 3 (16-40 microns), to water (200 ml) at 0°C and with stirring with Ystral agitation equipment. The rate of addition was 3 ml/min and the rate of stirring was 1500 r/min. The slurry obtained contained budesonide crystalline particles of MMD 4.2 microns. 90% of the particles had a diameter of below 8.6 μ m.

20 **Example 7**

A solution of lactose (2.0 g) in water was added via a peristaltic pump and through a glass filter, Pyrex no. 3, to a 20% solution of ethanol in methylethyl ketone, with stirring with Ystral agitation equipment. The rate of addition was 3 ml/min and the rate of stirring was 1500 r/min. The slurry obtained contained lactose particles of MMD 5.2 microns. 75% of 25 the particles had a diameter of below 10.0 μ m.

Example 8

A solution of salbutamol sulphate (1 g) in water (7 ml) was added via a peristaltic pump and through a glass filter, Pyrex no. 2, to a 20% solution of ethanol in methylethyl ketone at 30 room temperature, with stirring with Ystral agitation equipment. The rate of addition was 3

ml/min and the rate of stirring was 1500 r/min. The slurry obtained contained salbutamol sulphate crystalline particles of MMD 5.2 microns. 75% of the particles had a diameter of below 10.0 μ m.

Claims

1. A process for producing a pharmaceutical powder for inhalation comprising crystalline particles of an inhalation compound, comprising dissolving an inhalation compound in a solvent; and introducing the solution containing the inhalation compound in droplet form or as a jet stream, into an anti-solvent which is miscible with the solvent and which is under agitation, under non-supercritical conditions.
2. A process as claimed in claim 1 wherein the particles of the inhalation compound have a mass median diameter of 10 μm or less.
3. A process as claimed in claim 1 wherein the particles of the inhalation compound have a mass median diameter of 7 μm or less.
4. A process as claimed in claim 1 wherein the particles of the inhalation compound have a mass median diameter of at least 0.1 μm .
5. A process as claimed in claim 1 wherein the particles of the inhalation compound have a mass median diameter of at least 1 μm .
6. A process as claimed in claim 1 wherein the particles of the inhalation compound have a mass median diameter of 1-6 μm .
7. A process as claimed in claim 1 wherein at least 75% of the powder consists of particles having a diameter of 10 μm or less.
8. A process as claimed in claim 1 wherein at least 90% of the powder consists of particles having a diameter of 10 μm or less.

9. A process as claimed in any preceding claim wherein the solution containing the inhalation compound is introduced into the anti-solvent through a porous filter.
10. A process as claimed in any preceding claim wherein the solution containing the inhalation compound is introduced into the anti-solvent through one or more nozzles.
11. A process as claimed in any preceding claim wherein the solution containing the inhalation compound is substantially saturated or supersaturated.
- 10 12. A process as claimed in any preceding claim wherein the inhalation compound is selected from β_2 -adrenoreceptor agonists, anticholinergic bronchodilators, glucocorticosteroids, immunomodulators, anti-allergic drugs, expectorants, mucolytics, antihistamines, cyclooxygenase inhibitors, leukotriene synthesis inhibitors, leukotriene antagonists, PLA2 inhibitors, PKC-inhibitors, PAF antagonists and prophylactics of asthma, and pharmacologically acceptable esters and salts and/or hydrates thereof; and pharmaceutically acceptable additives.
13. A process as claimed in claim 12 wherein the inhalation compound is selected from β_2 -adrenoreceptor agonists and glucocorticosteroids.
- 20 14. A process as claimed in claim 13 wherein the inhalation compound is selected from salbutamol, salmeterol, formoterol, budesonide, terbutaline, fluticasone, rofleponide, and pharmaceutically acceptable esters and salts and/or solvates thereof.
- 25 15. A process as claimed in claim 14 wherein the inhalation compound is salbutamol sulphate.
16. A process as claimed in claim 14 wherein the inhalation compound is formoterol fumarate dihydrate.

17. A process as claimed in claim 14 wherein the inhalation compound is budesonide.

18. A process as claimed in claim 14 wherein the inhalation compound is terbutaline sulphate.

5

19. A process as claimed in claim 14 wherein the inhalation compound is rofleponide palmitate.

20. A process as claimed in claim 14 wherein the inhalation compound is salmeterol
10 xinafoate.

21. A process as claimed in any of claims 1-11, wherein the inhalation compound is a pharmaceutically acceptable additive.

15 22. A process as claimed in any of claims 1-11 wherein the inhalation compound is water-soluble, the solvent is water or another polar solvent or mixture of polar solvents, and the anti-solvent is a less polar solvent.

20 23. A process as claimed in claim 22 wherein the anti-solvent is selected from ethyl acetate, acetone, methyleethyl ketone, isopropanol or mixtures of 10-20% methanol, isopropanol or ethanol with 80-90% methyleethyl ketone or isopropanol.

25 24. A process as claimed in any of claims 1-11 wherein the inhalation compound is substantially water-insoluble, the solvent is less polar than the anti-solvent, and the anti-solvent is water or another polar solvent or mixture of polar solvents.

25. A process as claimed in claim 24 wherein the solvent is selected from methanol, isopropanol, dimethylsulphoxide, dimethylformamide, N'N'-dimethyl acetamide and phenol.

26. A process as claimed in any preceding claim wherein the solution containing the inhalation compound is added to the anti-solvent at a temperature of below 25°C.
27. A process as claimed in claim 26 wherein the solution containing the inhalation compound is added to the anti-solvent at a temperature of from 0°C to 5°C.
28. A process as claimed in any preceding claim wherein agitation of the anti-solvent is achieved by means of mechanical stirring, propellers, turbines paddles, anchor impellers or Ystral equipment, or by using ultrasound waves on or beside the filter or nozzles.
10
29. An inhalation compound obtainable by the process of any of claims 1-28.
30. A pharmaceutical powder for inhalation comprising crystalline particles of an inhalation compound obtainable by the process of any of claims 1-28.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00479

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/14, B01D 9/02, A61K 9/72
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0169618 A2 (STERILIZATION TECHNICAL SERVICES, INC.), 29 January 1986 (29.01.86) --	1-30
A	US 5314506 A (MICHAEL MIDLER, JR. ET AL), 24 May 1994 (24.05.94) --	1-30
A	WO 9003782 A2 (THE UPJOHN COMPANY), 19 April 1990 (19.04.90) -----	1-30

<input type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
• Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"B" earlier document but published on or after the international filing date	X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	& document member of the same patent family

Date of the actual completion of the international search <u>7 June 1996</u>	Date of mailing of the international search report <u>18 -07- 1996</u>
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer ANNELI JÖNSSON Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.	
PCT/SE 96/00479	

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0169618	29/01/86	SE-T3- 0169618 AU-B,B- 579166 AU-A- 4501285 CA-A- 1282405 CA-A- 2089075 EP-A,A,A 0544657 JP-B- 7002209 JP-A- 62027032 PT-A- 80494 US-A- 4826689 US-A- 4997454 WO-A,A- 9203380		17/11/88 22/01/87 02/04/91 22/02/92 09/06/93 18/01/95 05/02/87 22/11/85 02/05/89 05/03/91 05/03/92
US-A- 5314506	24/05/94	CA-A- 2044706 DE-D,T- 69112917 EP-A,A,B 0461930 ES-T- 2078447 JP-A- 4231960		16/12/91 15/05/96 18/12/91 16/12/95 20/08/92
WO-A2- 9003782	19/04/90	AU-B,B- 624421 AU-A- 4219889 DE-T- 68907062 EP-A,A,B 0437451 SE-T3- 0437451 HU-B- 209603 JP-T- 4500925 RU-C- 2026670		11/06/92 01/05/90 07/10/93 24/07/91 28/09/94 20/02/92 20/01/95